REMARKS

The elected Group I claims 1-3, 8-10, and 18-20 are pending, and claims 4-7, 11-17, and 21-26 are herein cancelled by applicants, the cancelled claims having been withdrawn by the Examiner pursuant to 37 C.F.R. 1.142 § (b). New claims 27-30 have been added.

Applicants thank the Examiner for correcting inventorship in compliance with 37 C.F.R. § 1.48(a), and pursuant to applicants' Petition to Correct Inventorship (*see* Office Action of 29 January 2003 at page 2, para 1).

Applicants acknowledge the Examiner's Claim *objections*, and have amended the subject claims accordingly to reflect proper dependancy.

Applicants acknowledge the Examiner's Specification *objections*, but are unable to identify any embedded hyperlinks or other form of browser-executable code.

Applicants acknowledge the Examiner's 35 U.S.C. § 112 ¶2 rejections, and have amended the subject claims accordingly to address binding affinity units and trademark usage.

Applicants acknowledge the Examiner's 35 U.S.C. § 112 ¶1 rejections, and have amended the subject claims accordingly to recite a requirement for *contiguous* amino acids.

Applicants acknowledge the Examiner's 35 U.S.C. § 102 (e), (a) and (b) rejections, and have amended the subject claims accordingly to exclude the asserted alleged prior art.

Additionally, applicants have amended the Sequence Listing, attached hereto as APPENDIX A, to include two additional SEQ ID NOS (SEQ ID NOS:11 and 12) to facilitate applicants' limiting amendments in response to the Examiner's 35 U.S.C. § 102-based rejections. No new matter has thereby been added, because SEQ ID NOS:11 and 12 are two species of the sequence genus represented by SEQ ID NO:1 and SEQ ID NO:2, respectively.

No new matter has been added.

FORMALITIES

Applicants are unable to identify any embedded hyperlinks or other form of browser-executable code. Applicants respectfully contend that any such alleged code must have been introduced by document 'scanning' at the USPTO (Office Action of 29 January 2003, at page 3, para 3).

Applicants have responsively amended the specification, as indicated above and discussed below, to clarify the units of binding affinity as is well known in the relevant art and as is supported by the originally filed specification. Additionally, applicants have amended the specification to reflect proper use of trademarks.

Applicants have prepared final formal drawings, attached hereto, in response to the Draftsperson's comments (*Id*, at page 11, para 13).

Claim Objections

The Examiner objected to claims 9 and 10 as being of improper dependent form (Office Action of 29 January 2003, at page 3, para 3).

Applicants have amended claims 9 and 10 to properly depend from claim 8, and respectfully request withdrawal of this objection.

Rejections under 35 U.S.C. § 112 ¶2

The Examiner rejected claims 1-3, 9,10 and 18 under 35 U.S.C. § 112, ¶2, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

First, the Examiner asserts that the recitation of "10^8" is relative and unclear because it lacks "units," (Office Action of 29 January 2003, at page 3, para 4).

Second, the Examiner asserts that claims 9 and 10 are indefinite in view of improper dependent form (*Id*).

Third, the Examiner asserts that the recitation of the trademark/trade name "HERCEPTIN®" in claims 3 and 10 is indefinite in that it is inappropriate to designate goods, as opposed to the source of such goods (*Id*).

First, applicants have amended independent claims 1 and 18 to recite "10^8 M^{-1}" in place of "10^8", and a conforming amendment has been made to independent claim 8. The applicable units are widely recognized in the art as being M^{-1}. Additionally, support for these amendments is found throughout the specification, and in particular at page 31, lines 19-20, and Figure 5C, which recite and show, respectively, that ECDIIIa peptides bind to intact 17-3-1 cells "at **nM** concentrations." Thus the degree of binding is detectable in the *nanomolar* range (*i.e.*, corresponding to a binding constant equal to or greater than 10^8 M^{-1}). Moreover, the specification is replete with references to 'binding' and 'high-affinity binding' and recites the intent to disclose novel high-affinity *binders* (*e.g.*,: the specification at page 1, lines 32-33; at page 2 , lines 28-31; at page 7, lines 18-19 (in relation to the binding data Figure 5); at page 8, line 7 (in relation to the binding data of Figure 7)).

Second, applicants have corrected an inadvertent dependency error, by amending claims 9 and 10 to properly depend from claim 8 and reflect proper antecedent basis.

Third, applicants have deleted the trademark HERCEPTIN from the subject claims.

Applicants, therefore, respectfully request withdrawal of the Examiner's § 112 ¶2 rejections with respect to amended claims 1-3, 8-10, and 18-20.

No new matter has been added.

Rejections under 35 U.S.C. § 112 ¶1

Written description

The Examiner rejected claims 1-3, 8-10 and 18-20 under 35 U.S.C. § 112, ¶1, as lacking adequate written description to "reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Specifically, the Examiner asserts the "disclosure of the specification fails to describe the genus of compounds encompassed by the claims," in essence because the claimed polypeptides "comprise amino acids in any order" (Office Action of 29 January 2003, at page 4, para 5).

Applicants have responsively clarified the subject matter by amending the subject claims to recite that the encoded 50 to 79 amino acid residues of SEQ ID NO:1, and the 80-419 residues of SEQ ID NO:2 must be *contiguous*. As amended, the subject genera in each case encompass polypeptides comprising a minimal *contiguous* amino acid sequence, and that have an affinity binding constant with respect to the HER-2 ECD of at least 10^8 M^{-1}."

Support for these amendments is found throughout the specification (*see, e.g.*, Specification at page 31, lines 11-23; Example 9, Figure 5; *and see* Specification at page 25, lines 13-16), where applicants have not only disclosed a "minimal" contiguous binding region, but have demonstrated its function in the context of much larger polypeptides; namely p68HER-2, and a sizable *diverse* fusion protein. The ECDIIIa sub-fragment tested in applicants' Example 9, for example, was expressed from the pET30a vector (Novagen) and thus represents a sizable *fusion* protein of ECDIIIa, comprising a heterologous amino terminal region of about 50 amino acids having: a poly-histidine tag; a thrombin cleavage site; an S-tag region; and an enterokinase site.

Additionally, recitation of "300" in originally submitted claim 8 was an inadvertent error, and independent claim 8 has been amended herein to recite "about 80 to 419 contiguous residues in length." Support for this amendment is found, *inter alia*, in the Specification at page 3, lines 15-31.

Applicants respectfully request withdrawal of the Examiner's asserted § 112 ¶1 written description rejection with respect to amended claims 1-3, 8-10 and 18-20.

No new subject matter has been added.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1-3, 8-10 and 18-20 under 35 U.S.C. **§ 102(e)** as being anticipated by **Doherty** et al. (U.S. Patent 6,414,130, issued 02 July 2002 with effective filing date of 20 January 1999) (Office Action of 29 January 2003, at page 6, para 7).

Specifically, the Examiner points out that Doherty discloses particular species of SEQ ID NOS:1 and 2 of the instant application, and thus discloses, at least in part, the instant claimed invention. Applicants acknowledge the Examiner's statement that because the parent application

lacks description of the novel variant amino acids disclosed in the instant continuation-in-part application, the filing date of the instant application, 16 February 2000, is used for purposes of comparison with the prior art (*Id*, para 6).

First, applicants have amended the Sequence Listing, attached hereto as APPENDIX A, to include two additional SEQ ID NOS (SEQ ID NOS:11 and 12) to facilitate applicants' further limiting amendments described immediately below. SEQ ID NOS:11 and 12 are two species of the sequence genus represented by the instant SEQ ID NO:1 and SEQ ID NO:2, respectively (*i.e.*, no new matter has been added).

Second, applicants have herein amended the subject claims to exclude the Examiner's alleged prior art. Specifically, independent claims 1 and 18 have been amended to recite "comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, and a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length, wherein..., and wherein the isolated polypeptide neither comprises SEQ ID NO:11, nor a fragment thereof of about 50 to 79 contiguous residues in length."

Likewise, independent claims 8 and 18 have been amended to recite "comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, and a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, wherein..., and wherein the isolated polypeptide neither comprises SEQ ID NO:12, nor a fragment thereof of about 80 to 419 contiguous residues in length."

Conforming amendments have been made to dependent claims, and to new claims 27-30.

Applicants, therefore, respectfully request withdrawal of the Examiner's 35 U.S.C. § 102(e) rejection with respect to amended claims 1-3, 8-10 and 18-20, in view of the fact that there is no overlapping subject matter with the asserted alleged prior art. New claims 27 -30, in view of the conforming language therein, are likewise clear of the asserted prior art.

The Examiner also rejected claims 1-3 and 8-10 under 35 U.S.C. § **102(a)** as being anticipated by **Doherty** et al. (Doherty et al., Proc. Nat. Acad. Sci, USA, 96(19):10869-10874, 1999, September) (Office Action of 29 January 2003, at page 7, para 8).

Specifically, the Examiner asserts that Doherty et al teach Herstatin, and that it may be glycosylated, thereby teaching the claimed inventions.

Without conceding as to whether this reference is valid prior art under § 102(a), applicants contend that in any event the amendments described above relating to the Examiner's § 102(e) rejection also suffice here to distinguish the alleged prior art, in view of the fact that there is no overlapping subject matter with amended claims 1-3 and 8-10. New claims 27 -30, in view of the conforming language therein, are likewise clear of the asserted prior art.

The Examiner also rejected claims 1, 3, 18 and 19 under 35 U.S.C. § **102(b)** as being anticipated by **Greene** et al (U.S. Patent 5,464,751; issued 07 November 1995) (Office Action of 29 January 2003, at page 7, para 9).

Specifically, the Examiner asserts that Greene et al teach NAF that binds to p185 HER-2 and, absent evidence to the contrary, may bind at a site different than antibody 4D5. The Examiner states that Greene et al also teach pharmaceutical compositions comprising NAF. Essentially, the Examiner states that because applicants' claims do not recite contiguous amino acids, they encompass the subject matter of Greene.

Applicants, as discussed above in relation to the Examiner's § 112, ¶1 based rejection, have amended the subject claims to recite that the encoded 50 to 79 amino acid residues of SEQ ID NO:1, and the 80-419 residues of SEQ ID NO:2 must be *contiguous*, thereby distinguishing the instant subject matter from the asserted prior art.

Applicants, therefore, respectfully request withdrawal of the Examiner's 35 U.S.C. § 102(b) rejection with respect to amended claims 1, 3, 18 and 19. New claims 27 -30, in view of the conforming language therein, are likewise clear of the asserted prior art.

The Examiner also rejected claims 1, 3, 10, 18 and 19 under 35 U.S.C. § **102(b)** as being anticipated by **Wels** et al (U.S. Patent 5,571,894; issued 05 November 1996) (Office Action of 29 January 2003, at page 8, para 10).

Specifically, the Examiner asserts that Wels et al teach recombinant antibodies that bind to extracellular domain of [c]e-erbB-2 (p185 HER-2) that may be glycosylated, and, absent evidence to the contrary, may bind at a site different than antibody 4D5. The Examiner states that Wels et al also disclose pharmaceutical compositions (*Id*, at page 9). Essentially, the Examiner states that because applicants' claims do not recite contiguous amino acids, they encompass the subject matter of Wels.

Applicants, as discussed immediately above, and in relation to the Examiner's § 112, ¶1 based rejection, have amended the subject claims to recite that the encoded 50 to 79 amino acid residues of SEQ ID NO:1, and the 80-419 residues of SEQ ID NO:2 must be *contiguous*, thereby distinguishing the instant claimed subject matter from the asserted prior art. Additionally, applicants have clarified the binding affinity units as discussed herein above in relation to the Examiner's § 112, ¶2 based rejection, thereby further distinguishing the instant claimed subject matter from the asserted prior art.

Applicants, therefore, respectfully request withdrawal of the Examiner's 35 U.S.C. § 102(b) rejection with respect to amended claims 1, 3, 10, 18 and 19. New claims 27 -30, in view of the conforming language therein, are likewise clear of the asserted prior art.

The Examiner also rejected claims 1, 3, 8, 10, 18 and 19 under 35 U.S.C. § **102(e)** as being anticipated by **Ring** (U.S. Patent 6,5054,561; issued 25 April 2000) (Office Action of 29 January 2003, at page 9, para 11).

Specifically, the Examiner asserts that Ring teaches antibodies that bind c-erbB-2, and, absent evidence to the contrary, may bind at a site different than antibody 4D5. The Examiner states that Ring also discloses pharmaceutical compositions (*Id*, at page 9). Essentially, the Examiner states that because applicants' claims do not recite contiguous amino acids, they encompass the subject matter of Ring.

Applicants, as discussed immediately above, and in relation to the Examiner's § 112, ¶1 based rejection, have amended the subject claims to recite that the encoded 50 to 79 amino acid residues of SEQ ID NO:1, and the 80-419 residues of SEQ ID NO:2 must be *contiguous*, thereby distinguishing the instant claimed subject matter from the asserted prior art.

Applicants, therefore, respectfully request withdrawal of the Examiner's 35 U.S.C. § 102(b) rejection with respect to amended claims 1, 3, 8, 10, 18 and 19. New claims 27 -30, in view of the conforming language therein, are likewise clear of the asserted prior art.

The Examiner also rejected claim 18 under 35 U.S.C. § **102(e)** as being anticipated by **Hudziak** (U.S. Patent 6,399,063; issued 04 June 2002; effective filing date of 25 January 1988) (Office Action of 29 January 2003, at page 10, para 12).

Specifically, the Examiner asserts that "Hudziak discloses pharmaceutical compositions comprising an antibody to HER-2 and a second agent, such as a cytokine (TNF-alpha, TNF-beta, IL-2, Interferon-gamma; citing col. 7, lines 3-61; claims 8-13), thereby disclosing the instant claimed pharmaceutical compositions.

Applicants respectfully *traverse* this rejection, because the instant genera of agents are neither anticipated by, nor obvious in view of any alleged genus of Hudziak. Specifically, applicants' invention is the first and only disclosure of the instant naturally occurring p185HER-2 binding proteins and antagonists. Thus, the instant genera are novel, and are neither anticipated by, nor obvious in view of any alleged second agent genus of Hudziak, the species of which do not bind to p185HER-2 and do not include fusion proteins; that is, the instant agents are not species of any Hudziak genus. This is particulary clear in view of applicants' amended recitation of contiguous amino acid residues as reiteratively discussed in detail above.

Moreover, even if they were species of an alleged encompassing Hudziak second agent genus (which they are not), the present novel species are not (could not possibly be) obvious in view of said genus and would therefore be patentably distinct even in view of said prior disclosed genus.

Furthermore, the fact that such a Hudziak second agent genus might *dominate* any aspect of the present subject matter is irrelevant in the sense of the present § 102 rejection, and applicants

need not take any position as to any such potential *dominance*. In fact, it is the applicants' position that the instant claimed genera do not comprise any species of Hudziak, and are, therefore, not dominated thereby.

Applicants, therefore, respectfully request withdrawal of the Examiner's § 102(e) rejection in view of amended claim 18.

Drawings

The Examiner has indicated a requirement that final corrected drawings accompany the instant Response and Amendment (Office Action of 29 January 2003, at page 11, para13).

Applicants have prepared final formal drawings, attached hereto, in response to the Draftsperson's comments. No new matter has been added.

Nonstatutory Double Patenting Rejection

The Examiner has provisionally rejected claims 1-3, 8-10 and 18-20 under the judicially created doctrine of obviousness-type double patenting; that is, as being unpatentable over claims 1-3, 8-10 and 18-22 of applicants' copending Application No. 09/234,208 (Office Action of 29 January 2003, at page 11, para 14).

Applicants respectfully request withdrawal of this *provisional* rejection in view of applicants' above-described amendments relating to the Examiner's § 102 based rejections, that eliminates overlap of the instant claimed subject matter with that of the asserted prior art, including that of applicants' copending Application No. 09/234,208.

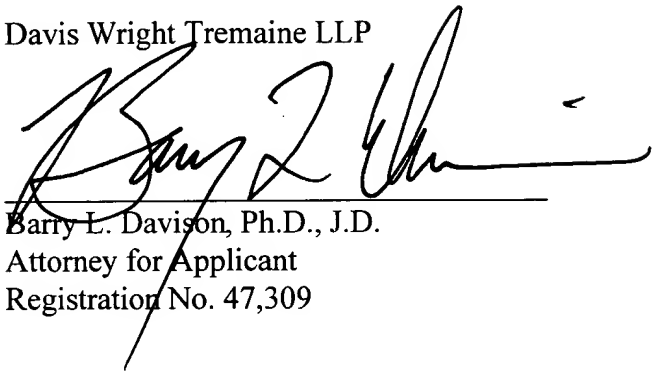
CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request allowance of the amended claim set (1-3, 8-10 and 18-20), and the new claims (27-30) provided herein above. The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

No new matter has been added. Entry of the Amendment is respectfully requested.

Respectfully submitted,

Davis Wright Tremaine LLP



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